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The Effect of Special Operations Training on Testosterone, Lean Body Mass, and Strength and the Potential for Therapeutic Testosterone Replacement: A Review of the Literature

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14. ABSTRACT

Special Operations Forces (SOF) are routinely exposed to physically demanding missions that result in significant changes in body composition, work capacity, and endocrine function. These changes primarily result from of an energy deficit and sleep deprivation, which are independently known to decrease levels of testosterone. The use of exogenous testosterone has been shown to increase lean body mass (LBM) and muscle function in healthy males and reverse cachexia in diseased populations. Therefore, the primary purpose of this review is to summarize and contrast literature in both SOF and non-military personnel on the relationships between a negative energy balance, sleep deprivation, and decreased testosterone. A secondary purpose is to summarize the effects of exogenous testosterone therapy in healthy males as well as to reverse the effects of muscle wasting diseases. A search of the literature from 1975-2015 utilizing search engines (i.e., PubMed) found 45 out of 70 relevant sources that directly addressed the primary or secondary purposes of this literature review. Data from these publications were summarized into tables providing mean observations. SOF training results in decreases in testosterone (-6.3%), LBM (-4.6%), and strength (-11.7%), which appear to be associated with an energy deficit (-3,351 kcal/day) and sleep deprivation (3 hours/day). Exogenous testosterone therapy increases LBM (6.2%) and strength (7.9-14.8%) and reverses cachexia (2.0%) and decreased strength (12.7%) in those suffering from diseases such as chronic obstructive pulmonary disease and human immunodeficiency virus. Therefore, the use of testosterone supplementation in SOF may attenuate changes in body composition and muscle function during SOF training or sustained operations.

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1.0 SUMMARY

The primary purpose of this review was to summarize and contrast literature in both Special Operations Forces (SOF) and non-military personnel on the relationships between a negative energy balance, sleep deprivation, and decreased testosterone. A secondary purpose was to summarize the effects of exogenous testosterone therapy in healthy males as well as to reverse the effects of muscle wasting diseases. A search of the literature from 1975-2015 utilizing search engines (i.e., PubMed) found 45 out of 70 relevant sources that directly addressed the primary or secondary purposes of this literature review. SOF training results in decreases in testosterone (-6.3%), LBM (-4.6%), and strength (-11.7%), which appear to be associated with an energy deficit (-3,351 kcal/day) and sleep deprivation (3 hours/day). Exogenous testosterone therapy increases LBM (6.2%) and strength (7.9-14.8%) and reverses cachexia (2.0%) and decreased strength (12.7%) in those suffering from diseases such as chronic obstructive pulmonary disease and human immunodeficiency virus. Therefore, the use of testosterone supplementation in SOF may attenuate changes in body composition and muscle function during SOF training or sustained operations.

2.0 INTRODUCTION

As reviewed previously, Special Operations Forces (SOF) are routinely exposed to prolonged and physically demanding missions that may result in significant physiological alterations, such as changes in body composition, work capacity, and endocrine function [1]. Researchers have suggested that the factors influencing these physiological changes are likely attributed to (1) the high physical demand placed upon SOF during both training and mission operations that necessitates high energy expenditure (EE), (2) a lower energy intake (EI), (3) a negative energy balance (EI-EE), and finally (4) sleep deprivation. For example, 8 weeks of Ranger training reportedly decreased body mass, fat mass, and lean body mass (LBM), with reductions in field measures of strength and power of 16-21% [2]. However, SOF training of as few as 3 days has been reported to markedly alter body composition and musculoskeletal function (Table 1).

Nindl and colleagues reported that 72-hour SOF training decreased body mass 3.1% and LBM 2.3%, with 9-15% decreases in lower body power [3]. Other investigators have reported that 8 days of SOF training or special support and reconnaissance resulted in decreases in body mass (3-4%), LBM (2-5%), and lower body strength or power of ~5-10% (Table 1). Interestingly, the decline in musculoskeletal function (strength and power) was consistently greater in magnitude but at the very least temporally related to decreased LBM. In addition to decreased LBM and strength, both shorter term combat exercise and SOF training have been shown to markedly alter hormonal function, specifically altering the hypothalamic pituitary gonadal (HPG axis), which may result in significant decrements in battlefield and training performance.

Collectively, data indicate that both prolonged SOF training ($\geq$ 3 weeks) and shorter term ($\leq$ 8 days) SOF training result in significant decreases in body mass and LBM, as well as reduced testosterone levels [2-10]. After 8 weeks of Ranger training, testosterone levels were reduced more than 80% in 50 males 24.6 $\pm$ 4.4 years of age [2]. Additionally, testosterone levels were decreased ~50% during participation in one of the U.S. Army's advanced military schools, the 3-week survival, evasion, resistance, and escape (SERE) training [8]. Both Ranger training and

SERE are physically and psychologically demanding, and participants are subject to a negative energy balance and sleep deprivation, which are both known to affect levels of testosterone. However, as with LBM and strength, significant reductions in testosterone are observed after only 3-8 days of SOF training (Table 1).

Table 1. Effects of Special Operations Training on Lean Body Mass and Muscle Strength

Source	Subjects		Duration (days)	EE (kcals/day)	EI (kcals/day)	Energy Balance	Sleep (h/day)	%Δ Testosterone	Δ BM (kg)	%Δ LBM	%Δ Lower Body Strength/ Power
	Age (yr)	n									
Nindl [3]	22±3	14	3	4,500	1,600	-2,900	3.6		-2.5	-2.3	-6.3
Morgan [8]	28.8±5	124	~3					-43			
Gomez-Merino [4]	21±2	26	5		3,200			-35			
Vaara [5]		52	5					-47	-1.6		
Aakvaag [6]	22-25	8	6	10,960	1,600	-9,360	2	-84	-4		-8.9
Welsh [7]	24±1	29	8	3,834	1,540	-2,294	NA	NA	-4.1	-2.4	
Kyröoläinen [9]	24±2	10	5-20	7,000-3,000	3,000	4,000-1,000			-4.2	-3.4	
Friedl [10]			96	4,000	2,800	-1,200	3.6	-88	-12.1	-7.3	
Friedl [10]			96	4,200	3,200	-1,000	3.6	-88	-10	-6.1	
Nindl [2]	24.6±4.4	50	96				2	-83	-10	-6.1	-20.0
Mean			***39.4***	***5,498.8***	***2,420***	***-3,351***	***3.0***	***-63***	***-6.1***	***-4.6***	***-11.7***

Δ = change; NA = not available.

Recently, Vaara et al. reported that after 7 weeks of basic and specialized training, neither body mass nor testosterone was affected in a group of 52 Finnish paratroopers [5]. However, in these same subjects, body mass and testosterone were decreased 2% and 47%, respectively, following a 5-day intensive combat course. Similarly, Aakvaag et al. reported that a 6-day combat training course at the Norwegian Academy of War reduced testosterone levels 83% [6], similar to the reduction reported after 8 weeks of Ranger training [2]. Due to the significant reductions in LBM and testosterone that occur within days of SOF training, the reductions in testosterone on decreased LBM and resulting impairments in muscle function appear to be related.

Investigations on SOF during 3- to 5-day intensive operational training report very high EE of between 5,000 and 10,000 kcals/day (Table 1). By comparison, a case report for an ultramarathon runner who ran continuously on a treadmill for 24 hours indicated that he consumed ~13,000 kcals [11]. Investigators derived these EE data using heart rate telemetry during the 24-hour run. Using similar methodology, Aakvaag and colleagues reported that EE in Norwegian cadets undergoing a 6-day combat course exceeded 10,000 kcals/day [6]. These high levels of EE have been associated with decreased testosterone levels (Table 1). In highly fit males (maximal oxygen consumption ~65 mL/kg/min), testosterone levels decreased 37% when training volume was doubled for 2 weeks [12]. This acute increase in training increased EE associated with training by ~100%. Therefore, it may be concluded that an acute increase in physical demand, resulting in an increase in EE, can reduce testosterone levels in fit highly males [12]. Training of SOF also results in a marked increase in EE; however, SOF training also includes the additional stress of a reduction in EI, resulting in a negative energy balance.

A negative energy balance may result from a reduction in EI, an increase in EE, or a combination of the two. Although intense short-term (<8 days) SOF training results in EE of up to 10,000 kcals/day, EI is reportedly as little as 1,600 kcals/day [3,6], resulting in an energy deficit (Table 1). Negative energy balances of 1,000-4,000 kcals/day have also been reported

during Ranger training [2]. In these examples of SOF training, the negative energy balance was accompanied by reduced testosterone levels. Similarly, during an acute 48-hour fast, where EI was eliminated, the HPG axis was disrupted as evidenced by decreases in luteinizing hormone (LH) and testosterone of 27.5% and 34%, respectively [13]. Therefore, consistent with literature on fasting, the energy deficit that occurs in SOF training or sustained special operations (SUSOPS) is likely an important factor in reducing testosterone.

On average, sleep during SOF training of 8 days or less is reportedly 2-4 hours/day and associated with decreases in testosterone (35-88%) and LBM (2-7%), as well as decreased muscle function of up to 20% (Table 1). Similarly, a 1-week reduction in sleep from an average of 8 hours/night to 5 hours/night reduced testosterone levels ~10% [14]. This reduction was independent of additional physical stress or negative energy balance, indicating sleep deprivation as a key factor in reducing testosterone during SOF training or missions.

Available research on military personnel during SOF training indicates that as little as 72 hours of exposure leads to decreased LBM and diminished muscular function (Table 1). Associated with these physiological impairments are marked reductions in testosterone levels (Table 1). The reductions in testosterone appear to be the additive effects of very high physical demand, reduced caloric intake, a negative caloric balance, and sleep deprivation. Each of these factors has separately been shown to reduce testosterone. Collectively, the resulting reduced functional capacity during SOF training likely occurs during SUSOPS and may impair mission success and endanger the safety of personnel. It is theorized that use of exogenous testosterone therapy in military personnel during SUSOPS is consistent with its use in patients suffering from wasting diseases or low LBM. During SUSOPS, the effects of physically demanding conditions, injury, a negative energy balance, and sleep deprivation may be attenuated by the use of supplemental testosterone, which may provide greater likelihood of mission success.

3.0 BACKGROUND

3.1 Testosterone Biochemistry

Testosterone is a steroid (lipid-based) hormone containing both androgenic and anabolic effects. The anabolic effect of testosterone is principally the stimulation of protein synthesis in muscle and bone, while the androgenic effects are the secondary sex characteristics (e.g., body hair, deepening of the voice, and male reproductive function). Testosterone is secreted by the testes in males of most mammalian species and to a much lesser extent the ovaries in females, as well as a small amount by the adrenal gland in both sexes [15].

The production of testosterone is regulated by the HPG axis. When testosterone levels are low, the hypothalamus releases gonadotropin releasing hormone, which stimulates the release of trophic factors in the anterior pituitary known as LH and follicle stimulating hormone (FSH). LH and FSH stimulate production of testosterone in the Leydig cells of the testes. As levels of testosterone increase, the levels of testosterone inhibit the release of gonadotropin releasing hormone, LH, and FSH by negative feedback systems.

Synthetic derivatives of testosterone, known as anabolic androgenic steroids (AAS), were developed in East Germany, and later American physician John Bosley Ziegler worked with Ciba Pharmaceutical Company to develop methandrostenolone (Dianabol™) in the United States [16]. AAS are principally testosterone molecules that have been modified in the 17 α carbon position, affecting liver metabolism of the compound, as well as the half-life, potency, and

toxicity of the synthetic compound. AAS bind to androgen receptors and stimulate the actions of testosterone and vary in delivery vehicle from oral and transdermal to injectable forms.

Typically, testosterone levels are 7-8 times greater in males than females, leading to the average physical size of males, particularly skeletal muscle and bone being significantly larger in males [17].

3.2 Testosterone Therapy

Exogenous testosterone therapy has shown modest benefits in anti-aging research as well as in combating type 2 diabetes and Alzheimer's disease. Males typically experience reductions in testosterone as a function of aging, resulting in low levels of LBM, while type 2 diabetics normally suffer from not only obesity but also lower levels of LBM. In addition, individuals living with human immunodeficiency virus (HIV) typically have low testosterone levels and may be treated with testosterone to combat fatigue [18]. In the case of HIV patients, it is likely that fatigue is at least in part related to decreased LBM impairing normal activities of daily living.

Studies investigating the effects of testosterone or AAS on skeletal muscle function have overwhelming employed male subjects. This is due to the potential unwanted androgenic effects resulting in masculinization in females. A majority of studies utilizing exogenous testosterone without the addition of resistance training [19-27] generally used subjects who were older than 40 years of age (mean age 46.3 years) (Table 2). However, male subjects in their 20s to 30s were more commonly studied [28-34] when resistance training was combined with exogenous testosterone treatment (Table 3).

Table 2. Effects of Testosterone on Lean Body Mass and Strength

Source	Subjects		Treatment Description		Treatment Group			Control Group		
						%Δ Strength			%Δ Strength	
	Age (yr)	n	Dosage (mg/wk)	Duration (wk)	%Δ LBM	Upper Body	Lower Body	%Δ LBM	Upper Body	Lower Body
Kido [19]	22.7±7.2	22	31.3	104	12.2	NA	NA	NA	NA	NA
Kenny [20]	76±4	67	35	52	1.8	NA	32.1	0.4	NA	22.4
Kenny [21]	77.9±7.3	69	35	52	1.9	2.0	2.9	0.4	4.4	-1.1
Hildreth [22]	66.5±5.8	47	70	52-104	1.6	12.4	12.8	0.2	7.3	12.2
Urban [23]	67±2	6	100	4	NA	NA	-25.2	NA	NA	NA
Bhasin [24]	28±3	12	125	20	2.9	NA	6.1	-4.9	NA	-0.4
Forbes [25]	22	7	200	12	12.0	NA	NA	NA	NA	NA
Griggs [26]	31.1±2.2	9	220	12	12.0	NA	NA	NA	NA	NA
Bhasin [24]	24±5	12	300	20	8.2	NA	19.5	-4.9	NA	-0.4
Frederiksen [27]	68	23	350	12	2.8	NA	NA	-0.2	NA	NA
Frederiksen [27]	68	23	350	24	2.6	NA	NA	-0.2	NA	NA
Bhasin [24]	25±4	13	600	20	12.3	NA	17.7	-4.9	NA	-0.4
Bhasin [31]	26±6	10	600	10	4.6	9.4	12.6	1.2	0.0	2.9
Mean	***46.3***		***232.0***	***28.5***	***6.2***	***7.9***	***14.8***	***-1.4***	***3.9***	***5.0***

Table 3. Effects of Testosterone or Anabolic Androgenic Steroid with Resistance Training on Lean Body Mass and Strength

Source	Subjects		Treatment Description			Training Intensity	Treatment Group			Control Group		
							%Δ LBM	%Δ Strength		%Δ LBM	%Δ Strength	
	Age (yr)	n	T or AAS	Dosage (mg/wk)	Duration (wk)			Upper Body	Lower Body		Upper Body	Lower Body
Hildreth [22]	66.5±5.8	49	T	70.0	52-104	Moderate	3.3	40.2	47.3	0.6	41.8	32.2
Alén [28]	28±5.8	4	T	180.0	24	Heavy	11.6	NA	19.4	0.3	NA	8.7
Friedl [29]	27±5	7	T	300.0	6	Moderate	4.7	22.3	4.5	NA	NA	NA
Giorgi [30]	27.8±7.4	11	T	300.0	12	Moderate	NA	21.4	NA	NA	9.0	NA
Bhasin [31]	30±7	11	T	600.0	10	Moderate	9.3	22.7	37.3	2.8	9.2	19.8
Mean	***35.9***			***290.0***	***13***		***7.3***	***26.6***	***27.1***	***1.2***	***20.0***	***20.2***
Freed [32]	18-30	6	AAS	85.0	6	Moderate	NA	~6.5	~6.5	NA	~4.0	~4.0
Alén [28]	29±5.8	4	AAS	220.0	24	Heavy	11.6	NA	19.4	0.3	NA	8.7
Freed [32]	18-30	7	AAS	260.0	6	Moderate	NA	~12.3	~12.3	NA	~4.0	~4.0
Friedl [29]	27±5	7	AAS	300.0	6	Moderate	2.6	11.5	2.6	NA	NA	NA
Hervey [33]	25-38	7	AAS	700.0	6	Moderate	4.4	13.5	16.6	0.0	5.1	-4.0
Hervey [34]	19-25	11	AAS	700.0	6	Moderate	3.5	NA	NA	-0.6	NA	NA
Mean	***26.3***			***377.5***	***9***		***5.5***	***12.5***	***12.9***	***-0.1***	***5.1***	***2.4***

T = testosterone.

As summarized in Tables 2 and 3, exogenous testosterone or AAS has been administered for as few as 4 weeks [23] or up to 24 months in duration [19,22]. The average dosage used in studies investigating exogenous testosterone treatment was ~250-300 mg weekly, for an average of 35-40 weeks (Tables 2 and 3). Dosages of AAS do not correlate directly with testosterone dosages and vary in potency from one AAS to another. However, studies administering AAS typically lasted ~10 weeks using nearly 400 mg of AAS weekly, and in healthy subjects included a resistance-training component (Table 3).

Numerous forms of delivery have been developed for exogenous testosterone. These include injectable forms of testosterone, tablets, buccal administration, transdermal patches, subcutaneous pellets, and topical gels. An extensive review by Margo and Winn [18] indicates that injectable forms of testosterone are generally less expensive and result in fewer side effects than other delivery modalities. In the present investigation, studies reviewed utilized testosterone injections when supplementing testosterone whether in younger adult males (Tables 2 and 3), older adult males (Tables 2 and 3), or patients with HIV [35-39] or chronic obstructive pulmonary disease (COPD) [40] or those undergoing dialysis [41].

The most definitive measure of muscle enlargement (hypertrophy) is the use of a needle biopsy and histology. However, the most common indirect measure of changes in muscle mass is the measurement of LBM. Body composition assessment, such as the use of skinfold calipers or air displacement plethysmography (BodPod™), yields a body fat percentage for subjects. An individual's body mass (BM) is the sum of both fat mass (FM) and LBM, where FM=BM * % body fat. LBM is then calculated as the remainder (BM=FM + LBM).

Resistance training of sufficient intensity and volume increases LBM and strength. Numerous studies have employed a resistance-training component to investigate the additive effects of testosterone or AAS on musculoskeletal function, particularly LBM and strength. Intensity of training was moderate to heavy in these studies as described by the investigators (Table 3). Investigations utilizing exogenous testosterone and resistance training were generally longer in duration (~40 weeks) when compared to studies employing AAS and resistance training, with a mean duration of ~10 weeks (Table 3).

4.0 RESULTS

4.1 Testosterone

Exogenous testosterone administration, independent of resistance training, increased LBM. Results indicate that on average LBM increased 6.2% following ~38 weeks of testosterone treatment (Table 2). The magnitude of the increase in LBM appeared to be a function of the dosage of testosterone administered. In the studies reviewed presently, testosterone doses of less than 125 mg/week reported increases in LBM of ~2%. In contrast, dosages of at least 200 mg/week to as much as 600 mg/week increased LBM as much as 12%. Increased LBM as a function of testosterone treatment was further modulated by the duration of treatment.

Bhasin and colleagues utilized a high dose of exogenous testosterone (600 mg/weekly) in two separate studies, reporting a 4.6% increase in LBM after 10 weeks and 12.3% after 20 weeks in young adult males, suggesting that doubling the duration of the study increased the change in LBM [24]. Interestingly, Kido and colleagues used a low dosage of testosterone (~30 mg/week) for 24 months [19]. This dosage of testosterone is well below the apparent effective threshold of 200 mg/week discussed previously. However, they reported a 12.2% increase in LBM after 24 months. Therefore, both the dose and duration of treatment appear to affect the increase in LBM. In addition, the age of the subjects appeared to influence the effect of testosterone to increase LBM.

The increase in LBM as a result of exogenous testosterone treatment was markedly lower in older subjects (Table 2). Hildreth et al. recently reported that 12-24 months of testosterone treatment in older men (66.5 ± 5.8 years) increased LBM less than 2% [22]. However, the dose used (~70 mg/week) is less than the threshold of 200 mg/week described above. Frederiksen and colleagues treated older subjects (mean age 68) with 350 mg/week of testosterone for up to 6 months, reporting an increase in LBM of 2.6% to 2.8% [27]. In contrast, Bhasin et al. utilized a similar dose of testosterone (300 mg/week) for 20 weeks and reported that LBM increased 8.2% in young adult males (24 ± 5 years of age) [24]. The response in younger adult males 20-30 years old, specifically to increased LBM as a result of testosterone treatment, appears to be far greater when compared to men ≥ 60 years old.

The average change for upper body and lower body strength following testosterone administration was 7.9% and 16.1%, respectively (Table 2). Collectively, data on younger adult males (age 20-30 years) appear to suggest that the change in strength, particularly lower body strength, was related to the change in LBM. Lower body strength may be more relevant to the demands of SOF who must carry heavy gear for prolonged periods. As reported previously, LBM increased as a function of dose. Similarly, lower body strength increased more with increasing dosages (Table 2). For example, 20 weeks of 125 mg/week testosterone resulted in increases in LBM and strength of 2.9% and 6.1%, respectively, whereas 20 weeks of 300 mg/week testosterone resulted in increased LBM and strength of 8.2% and 19.5%, respectively [24]. However, it should be noted that data do not necessarily support a direct correlation between LBM and strength in older subjects.

Long duration (≥ 12 months) of low doses (≤ 70 mg/week) of testosterone increased LBM less than 2% in male subjects over 60 years of age [19-22]. However, lower body strength was reported to increase by as much as 32% in these subjects (Table 2). In younger subjects, the increase in strength was likely due to an increase in mass, whereas in older subjects long-

duration, low-dose testosterone treatment appeared to affect the efficiency of existing muscle to generate force.

4.2 Testosterone and Resistance Training

Moderate intensity resistance training and an average of 290 mg/week of testosterone increased LBM, upper body strength, and lower body strength 7.3%, 26.6%, and 27.1%, respectively (Table 3). In contrast, resistance training alone increased LBM, upper body strength, and lower body strength 1.2%, 20%, and 20.2%, respectively. Collectively, these data indicate an additive effect of testosterone to increase strength and LBM. Although fewer studies are available at present, evidence suggests that results are affected by (1) higher doses, (2) longer duration, and (3) intensity of training (Table 3).

4.3 AAS and Resistance Training

Moderate intensity resistance training combined with AAS (378 mg/week) for ~10 weeks increased LBM, upper body strength, and lower body strength 5.5%, 11%, and 11.5%, respectively (Table 3). In contrast, resistance training combined with a placebo changed LBM, upper body strength, and lower body strength -0.1%, 4.4%, and 3.2%, respectively. Collectively, these data indicate an additive effect of AAS to increase strength and LBM.

Both testosterone and AAS have an additive effect to increase LBM and strength when compared to strength training alone. This additive effect can be seen in as few as 6 weeks [29,32-34]. In addition, it appears that AAS, when compared to testosterone, has less of an effect on body composition and strength. However, in the present review, studies using AAS generally lasted 6 weeks, whereas studies using testosterone were normally 10 weeks or longer. Consistent with this shorter duration, subjects treated with an AAS placebo had less of a response to resistance training than control subjects in studies using testosterone and resistance training. Therefore, due to relatively large differences in the duration of AAS and testosterone studies, direct comparisons of the efficacy to increase LBM and strength are difficult.

4.4 Testosterone and AAS in Diseased Populations

4.4.1 Testosterone. Both testosterone and AAS have been used therapeutically to prevent cachexia, muscle wasting, and fatigue in patients living with HIV and COPD, as well as those undergoing dialysis (Table 4). As with healthy populations, some studies using patients with COPD and HIV incorporated resistance training; however, the overwhelming majority did not (Table 4). Fatigue and diminished work capacity, likely associated with cachexia and muscle wasting, are common symptoms in these populations, particularly those living with HIV [18].

Use of exogenous testosterone (~150 mg/week) for ~12 weeks increased LBM and strength 4.1% and 12.7%, respectively (Table 4). Casaburi et al. incorporated resistance training and 100 mg/week of exogenous testosterone in a 10-week study of patients suffering from COPD [40]. Strength increased in both treated and control subjects, 21.0% and 16.2%, respectively. However, LBM increased 6.3% in the testosterone group but was unchanged in the control group (Table 4). As with healthy subjects, these data indicate an additive effect of testosterone and resistance training to increase LBM and strength in diseased patients.

Cachexia, decreased LBM, and decreased strength occur within days of SOF training, while diseases such as COPD and HIV lead to similar physiological changes over time. Therefore, the use of testosterone to increase LBM and muscle strength in diseased patients suggests that testosterone supplementation may attenuate changes in body composition and strength in SOF during training or SUSOPS.

Table 4. Effects of Testosterone or Anabolic Androgenic Steroid on Body Mass, Lean Body Mass, and Strength in Patients with Disease or Muscle Wasting

Source	Subjects		Treatment Description				Disease	Treatment Group			Control Group		
	Age (yr)	n	T or AAS	Resistance Training	Dosage (mg/wk)	Duration (wk)		%Δ BM	%Δ LBM	%Δ Strength	%Δ BM	%Δ LBM	%Δ Strength
Casaburi [40]	66.6±7.5	12	T	No	100	10	COPD	1.7	4.4	12.1	-0.4	-0.4	2.2
Casaburi [40]	66.4±7.2	11	T	Yes	100	10	COPD	2.4	6.3	21.9	0.1	0.4	16.2
Gold [35]	40.4±9.4	66	T	No	125	12	HIV	1.5	1.5	NA	0.8	0.4	NA
Knapp [36]	43.7±7.4	30	T	No	300	16	HIV	2.3	4.4	4.2	0.5	0.3	1.6
					156.3	***12.0***		***2.0***	***4.1***	***12.7***	***0.3***	***0.2***	***6.7***
Gold [35]	41.7±8.8	157	AAS	No	75	12	HIV	3.4	2.9	NA	0.8	0.4	NA
Grunfeld [37]	41.1±9.0	64	AAS	No	140	12	HIV	2.7	NA	NA	1.7	NA	NA
Johansen [41]	55.7±13.4	19	AAS	No	152	12	DIA	3.9	7.2	10.8	0.0	-0.4	4.2
Johansen [41]	55.5±12.5	20	AAS	Yes	165	12	DIA	2.6	6.1	49.1	2.0	-0.8	61.4
Grunfeld [37]	40.1±7.5	65	AAS	No	280	12	HIV	4.3	NA	NA	1.7	NA	NA
Grunfeld [37]	39.5±7.5	68	AAS	No	560	12	HIV	3.5	NA	NA	1.7	NA	NA
Hengge [38]	41.4	30	AAS	No	700	16	HIV	5.3	5.1	NA	1.6	1.0	NA
Hengge [38]	37.3	31	AAS	No	1050	16	HIV	4.5	3.3	NA	1.6	1.0	NA
Ferreira [39]	70.3±1.5	10	T&AAS	No	110	9	HIV	3.9	6.8	NA	-0.9	1.5	NA
Mean	***49.2***				***359.1***	***12.6***		***3.8***	***5.2***	***29.9***	***1.1***	***0.4***	***32.8***

DIA = dialysis.

4.4.2 Anabolic Androgenic Steroids. Numerous investigations have studied the effects of AAS (~359 mg/week) to increase LBM and strength in patients with HIV or COPD or in those undergoing dialysis (Table 4). Collectively, these studies indicate that ~12.5 weeks of AAS increased LBM 5.2%. Independent of dose, research in patients living with HIV indicates that AAS consistently increased both body mass and LBM. To date, little information is available with regard to the functional outcomes (e.g., increased strength) when attenuating cachexia in these subjects; however, given the increase in LBM, it is reasonable to infer an increase in strength.

5.0 DISCUSSION/CONCLUSIONS

Both SOF training and SUSOPS involve high physical demand for days accompanied by a negative energy balance and sleep deprivation, compounding risk for cachexia and fatigue that may impair mission success. Reports have indicated that SOF training, simulating conditions experienced during SUSOPS, results in an average 6.7-kg decrease in body mass after an average of 44 days of operations (Table 1). High daily energy expenditures coupled with reduced daily caloric intake result in a large negative energy balance (> 3,000 kcals/day) consistent with decreased body mass (Table 1). These operational conditions and resulting anthropometric changes bear similarity to the experimental conditions of overtraining and caloric restriction which, specifically in males, impair the HPG axis leading to markedly decreased testosterone levels. In addition, reductions in sleep to an average 3 hours/day likely compound reduction in HPG function from physical demand and negative energy balance.

5.1 Physical Demand

High levels of physical demand reportedly suppress testicular function. Five days of combat training exercises in Norwegian cadets reduced circulating testosterone 84%. The caloric expenditure of these combat exercises was estimated at more than 10,000 kcals/days. Roberts and colleagues studied the effect of acute overtraining on testicular function in highly trained males (maximal oxygen consumption of 65.4 ± 3.6 mL/kg/min) [12]. The subjects' level of fitness ranks in the top 1% according to the American College of Sports Medicine [42]. A 2-week doubling in their training volume dramatically reduced testosterone levels (36%). The fitness level of elite SOF is reportedly comparable to that of highly trained endurance athletes [1]. Therefore, even in very fit individuals, highly stressful physical demands appear to reduce HPG function, and collectively the data suggest that the demanding physical nature of SOF training and SUSOPS can reduce testosterone levels, particularly when coupled with a negative energy balance and sleep deprivation.

5.2 Negative Energy Balance

Evidence clearly points to a large energy deficit during SOF training (Table 1). A negative energy balance averaging more than 3,000 kcals/day during SOF training is consistent with weight loss of nearly 7 kg (Table 1). It should be noted that the negative energy balance results not just from a reduction in EI, but primarily is due to the very large EE of SOF training that may exceed 10,000 kcals/day. During SOF training, EI varies from as little as 1,600 kcals/day to ~3,000 kcals/day, but does not match EE. It is therefore unlikely that food could be supplied and consumed at a rate to match this level of EE incurred during SOF training, making a negative energy balance inevitable.

Acute caloric restriction (fasting) in men has been shown to disrupt endocrine function [13]. Specifically, a negative energy balance has been shown to disrupt the HPG axis as evidenced by decreased LH and testosterone levels. Because a fast of 48 hours can result in significant depression of testosterone without significant changes in body mass or body composition, it appears that the decrease in testosterone resulting from a negative energy balance precedes alterations in body composition. Due to the profound effect of testosterone on protein synthesis, it is logical to conclude that the decrease in testosterone resulting from a negative energy balance is at least partly responsible for diminished LBM and musculoskeletal function.

5.3 Sleep Deprivation

Sleep deprivation is commonly cited as a factor associated with difficulties experienced during SOF training and SUSOPS. Daily sleep has been estimated to be just 2-4 hours during SOF training (Table 1). Sleep deprivation may also include psychological stresses such as realistic battlefield simulations and captivity. It is clear that both sleep deprivation and decreased HPG function occur at least temporally during SOF training and likely during SUSOPS. A modest reduction in normal sleep volume from 8 to 5 hours daily reduces testosterone levels after 1 week in healthy young males [14], suggesting that the significant sleep deprivation experienced during SOF training is a key factor in the reduction of testosterone.

5.4 Testosterone Therapy

Data clearly demonstrate the additive effects of testosterone or AAS to increase LBM and strength when combined with resistance training (Table 3). However, testosterone independent of resistance training has been reported to increase LBM and strength (Table 2). More importantly, in diseased populations (e.g., COPD, HIV) exhibiting cachexia, low LBM, and fatigue, the use of testosterone or AAS reportedly increases LBM and strength while control subjects continue to suffer losses in LBM and strength (Table 4). Therefore, the use of exogenous testosterone or AAS may reverse or attenuate cachexia and diminished muscle function in SOF during or following SUSOPS.

6.0 RECOMMENDATIONS

Data support the relationship between altered HPG function and decreases in LBM and functional capacity during SOF training. Further, it appears that reductions in testosterone precede alterations in body composition or muscle function. High physical demand, negative energy balance, and sleep deprivation all appear to affect testosterone levels. However, the seeming inevitability of a large negative energy balance during SOF training indicates that investigations incorporating a negative energy balance and testosterone therapy are warranted in both experimental animal models and human subjects. In animal models, caloric restriction can be used to create a negative energy balance, while studies in human models should use both an increase in EE and a reduction in EI to create a caloric deficit. Reduced sleep can also be incorporated into these studies to ascertain the additive nature of caloric deficit and sleep deprivation on LBM and strength.

7.0 LIMITATIONS

The use of exogenous testosterone or AAS has been linked to a number of sporting scandals including Canadian 100-meter champion Ben Johnson in the 1988 Olympics [43]. The effects of testosterone and AAS to increase LBM and strength are well known, and in 1990 the U.S. Congress passed the Anabolic Steroid Control Act, classifying both testosterone and AAS as controlled substances [44]. A direct relationship between testosterone levels and aggressive or criminal behavior is not well founded. Studies do not conclusively support that aggressive or anti-social behavior in males is linked to higher levels of testosterone. [45]. Further, evidence to support concepts such as “roid rage” from the use of testosterone or AAS is often complicated by the use of additional drugs, whether licit or illicit, and reported incidences of criminal or anti-social behavior.

Although days of demanding SOF training may result in reduced testosterone that arguably contributes to decreased LBM, at present little data exist on the effects of short-term testosterone therapy on LBM and strength. A majority of studies supplementing testosterone or AAS with or without resistance training treated subjects well in excess of 6 weeks. It is unknown whether days of testosterone therapy would reverse or attenuate the anthropometric and functional changes associated with SOF training.

One of the most glaring limitations of exogenous testosterone therapy in SOF would be its use in females entering SOF. The androgenic effects of testosterone in female candidates entering SOF training would likely be an unwelcome risk, particularly in terms of disrupting the

normal female HPG axis and the potential for the development of male secondary sex characteristics in females. This limitation is unavoidable and should not discount the potential benefit of short-term exogenous testosterone to assist the combat performance of males in SOF. Data specific to changes in females during SOF training and SUSOPS need to be gathered and strategies developed to attenuate losses in LBM and strength in female SOF.

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LIST OF SYMBOLS, ABBREVIATIONS, AND ACRONYMS

Δ	change
AAS	anabolic androgenic steroids
BM	body mass
COPD	chronic obstructive pulmonary disease
DIA	dialysis
EE	energy expenditure
EI	energy intake
FM	fat mass
FSH	follicle stimulating hormone
HIV	human immunodeficiency virus
HPG	hypothalamic pituitary gonadal
LBM	lean body mass
LH	luteinizing hormone
NA	not available
SERE	survival, evasion, resistance, and escape
SOF	Special Operations Forces
SUSOPS	sustained special operations
T	testosterone